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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,824	CHEN ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *11-16,22,29-31,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,17-2123-28 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/17/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to ILIA OUSPENSKI, Group Art Unit 1644, Technology Center 1600.

2. Applicant's amendment/remarks, filed 03/27/2006, are acknowledged.

Claims 1 – 34 are pending.

3. Applicant's election with traverse of Group I (claims 1 – 12, 14, 17 – 30, and 32, drawn to methods for treating autoimmune disease using a 4-1BB agonist that is an antibody or a ligand) in the reply filed on 03/27/2006 is acknowledged.

Applicant further elects the Species of systemic lupus erythematosus as the autoimmune disease and the Species of an antibody as the 4-1BB agonist. Applicant submits that the elected species read on claims 1 – 10, 17 – 21, 23 – 28, and 32.

The traversal is on the grounds that the restriction, as set forth in the prior Office Action, mailed 02/23/2006, is allegedly improper. Applicant does not provide substantive reasoning or grounds for this assertion.

The requirement is still deemed proper, for the reasons set forth in the prior Office Action, and is therefore made FINAL.

4. Claims 11 – 16, 22, 29 – 31, and 33 – 34 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 1 – 10, 17 – 21, 23 – 28, and 32 are under consideration in the instant application, as they read on the elected invention drawn to methods for treating systemic lupus erythematosus using a 4-1BB agonist antibody.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The provisional application USSN 60/395,896 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application, except as set forth herein.

The provisional application USSN 60/395,896 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claim 17 of this application. Specifically, insufficient support was identified for the step of "monitoring" the subject for symptoms of a disease. Consequently, claim 17 has been accorded the priority of the filing date of the instant application, i.e. 07/14/2003.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

6. Applicant's IDS, filed 09/17/2004, is acknowledged, and has been considered.

7. Claim 7 is objected to because of the following informalities: an apparent typographical error in "interferon-K," where apparently "interferon-γ" has been intended.

Claims 8 and 9 are objected to because of the following informalities: the claims include a recitation of "Gr-1," while the specification refers to apparently the same molecule as "GR-1"(e.g. page 30, first paragraph).

Appropriate correction or clarification is required.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 6, 8, 9, and 21 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 6 and 21 are indefinite in the recitation of antibody "2A" because its characteristics are not known. The use of "2A" as the sole means of identifying the claimed antibody renders the claim indefinite because 2A is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct biological materials. Amending the claims to recite the appropriate Deposit Accession Number would obviate this rejection.

B. Claims 8 and 9 are indefinite in the recitation of "Gr-1," because its characteristics are not known. The use of "Gr-1" as the sole means of identifying the

polypeptide renders the claim indefinite because the designation "Gr-1" is used by others in the art to denote unrelated materials (e.g. Anukam et al., 2006, Microbes and Infection, March 29, pages 1 – 5; see entire document, in particular, e.g. the Title).

Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 6 and 21 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

It is apparent that the "2A" antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line or a hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

12. Claims 1 – 9, 17 – 21, 23 – 27, and 32 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method of depleting, or inducing death of, double negative T cells in a subject having systemic lupus erythematosus, does not reasonably provide enablement for depleting, or inducing death of, double negative T cells in a subject having a generically recited autoimmune disease, lymphoproliferative disease, or allergy.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

It is noted that the elected invention is limited to methods for depleting, or inducing death of, double negative T cells in systemic lupus erythematosus; however, the rejection is set forth with regard to the full scope of the generic claims as presently recited.

The specification does not enable one of skill in the art to deplete, or induce death of, double negative T cells in a subject having an autoimmune disease, a lymphoproliferative disease, or an allergy, by administering an antibody that binds to 4-1BB, as claimed, without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

In evaluating the facts of the instant case, the following is noted: In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive antibodies can be species- and model-dependent, it is not clear that reliance on the experimental observations in the experimental model described in the instant specification provide the basis for employing antibodies to 4-1BB for treating any autoimmune diseases, lymphoproliferative disease, or an allergy. For example, Blazar et al. (J. Immunol., 1996, 157: 3250 – 3259; see entire document, in particular, e.g. page 3257, column 2 first paragraph) disclose that issues such as tissue distribution, half-life, affinity and avidity obtained with various antibodies targeting costimulatory molecules might prove to be highly important in achieving a therapeutic effect. Thus any conclusion regarding the efficacy of T and/or B cell modulation in a pathological condition should be interpreted in light of the specific disease being treated. Therefore, there is no evidence that the animal model used in the experiments disclosed in the specification would be predictive of the therapeutic methods encompassed by the claims.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently

short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of insufficient guidance by the instant specification and the lack of predictability of the art to which the invention pertains with respect to the 41-BB signaling pathway, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of the clinical protocols, and absent working examples providing evidence tat the claimed methods are effective for depleting, or inducing death of, double negative T cells in a subject having an autoimmune disease, a lymphoproliferative disease, of an allergy, other than in systemic lupus erythematosus.

13. Claims 1 – 5, 7 – 10, 17 – 20, 23 – 28, and 32 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods employing a 4-1BB agonist antibody 2A, with or without an antibody that binds to GR-1, does not reasonably provide enablement for methods employing a generically recited "4-1BB agonist" or "GR-1 binding agent." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

It is noted that the elected invention is limited to 4-1BB agonist antibodies; however, the rejection is set forth with regard to the full scope of the generic claims as presently recited.

The specification discloses working examples of using a 4-1BB agonist antibody to deplete specific populations of T and B cells in a mouse model of SLE, while the instant claims encompass in their breadth any "4-1BB agonist." Likewise, anti-GR-1 antibody is the only GR-1 binding agent exemplified in the specification.

A person of skill in the art is not enabled to make and use any agonist of 4-1BB, or any GR-1 binding agent, commensurate with the scope of the claims as presently recited, because it was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "agonists" or "binding agents." Huang (Pharmacology and therapeutics, 2000, 86: 201 – 215; see entire document) reviews e.g. on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein function, and notes that the process requires long periods of trial and error testing. The structure of such molecules cannot be readily envisioned by one of skill in the art based upon the guidance provided in the specification as-filed. Therefore, Applicant does not provide a sufficiently enabling disclosure regarding how to make and use 4-1BB agonists other than antibodies that bind to 4-1BB.

Furthermore, a person of skill in the art is not enabled to practice the claimed methods with a generically recited "4-1BB agonist" or "antibody that binds to 4-1BB," other than the specific antibody "2A" disclosed in the specification, for the following reason:

Chen et al. (US Pat. Pub. No. 2005/0013811; see entire document) teach and claim methods of generating an enhanced immune response in a subject, comprising administering an agonistic 4-1BB-binding agent, such as an antibody that binds to 4-1BB (see entire document, in particular, e.g. claims 1 and 2). Since enhancing immune response is the opposite effect of the one instantly claimed, it is unpredictable whether an agonistic 4-1BB-binding agent, and in particular an agonistic anti-4-1BB antibody,

would achieve enhancement of an immune response (and thus exacerbation of an autoimmune disease), as claimed by Chen et al., or suppression of an immune response, such as depletion of double negative T cells, as claimed in the instant application.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the structural features of "agonists" are unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970). "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a)

shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1 – 5, 17 – 20, 23 – 27, and 32 are rejected under **35 U.S.C. 102(b)** as being anticipated by Kang et al. (US Patent No. 5,928,893; 1999; reference AD on IDS filed 09/17/2004; see entire document).

Kang et al. teach treatment of autoimmune diseases by administering a monoclonal antibody to human 4-1BB (see entire document, in particular, e.g. column 12 lines 33 – 42). Kang et al. also teach that antibodies to 4-1BB have immunosuppressive activity in vitro (e.g. column 11 lines21 – 27, and Figure 6).

Since Kang et al. teach administering an antibody of the same specificity as the instant application, to the same patient population as the instant application, the functional properties of the antibody (i.e. agonist) and the mechanism of action (i.e. depleting, or inducing death of, double negative T cells) are inherently the same.

Claim 17 is included in the rejection, because treating a disease inherently includes monitoring the symptoms.

Therefore, the reference teachings anticipate the instant claimed invention.

16. Claims 1 – 5, 10, 17 – 20, 23 – 28, and 32 are rejected under **35 U.S.C. 102(a) and 102(e)** as being anticipated by B. Kwon (US Patent No. 6,303,121; 2001; reference AF on IDS filed 09/17/2004; see entire document).

Kwon teaches monoclonal antibodies against human 4-1BB, which can be used to suppress T cell proliferation and activation (see entire document, in particular, e.g. column 5 lines 22 – 26). Kwon further teaches that agonist antibodies to 4-1BB can be used therapeutically in systemic lupus erythematosus (e.g. column 5 lines 50 – 59).

Since Kwon teach administering a functionally equivalent antibody (i.e. agonist) to 4-1BB to the same patient population as the instant application, the mechanism of action (i.e. depleting, or inducing death of, double negative T cells) of antibodies taught by Kwon is inherently the same as that of instantly claimed antibodies.

Claim 17 is included in the rejection, because treating a disease inherently includes monitoring the symptoms.

Therefore, the reference teachings anticipate the instant claimed invention.

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Aruffo et al., US Patent No. 6,210,669; 2001; reference AE on IDS filed 09/17/2004; see entire document, in particular, e.g. Example XI at column 10).

The reference teaches that administering anti-4-1BB antibodies blocks development of experimental autoimmune encephalomyelitis, a method which does not appear to be patentably distinct from those instantly claimed.

18. Conclusion: no claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

May 25, 2006

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
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5/25/06